UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/093,972	06/09/98	NYCE J	P6641031

HM12/0104

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EXAMINER	
EPPS, J	
ART UNIT	**PAPER NUMBER**
1635	17

DATE MAILED: 01/04/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/093,972	Johnathan Nyce
Examiner	**Group Art Unit**
Jan t Epps	1635

☒ Responsive to communication(s) filed on *Sep 24, 1999*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-107* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-107* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *4*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

DETAILED ACTION

Sequence Listing

1. The Declaration submitted under 37 CFR 1.821(f) is unacceptable, Applicant's representative stated that the paper and computer readable copies of the sequence listing submitted in accordance with 37 CFR 1.821(c) and 1.821(e), "include no significant new matter and are, to the best of the applicant's knowledge, substantially the same as the sequence submitted with the application as filed". This statement is unacceptable, as indicated on the Notice to Comply mailed 8/24/99 Applicants were requested to provide a statement that the content of the paper and computer readable copies are the same, and where applicable, include no new matter, as required by 37 CFR 1.821(e)-(g) or 1.825(b) or 1.825(d).

2. The reply filed 11-22-99 is not fully responsive to the communication mailed 8-24-99 for the reason(s) set forth on the attached Notice To Comply With The Sequence Rules or CRF Diskette Problem Report.

Election/Restriction

3. Applicant's election with traverse of Group I in Paper No. 7 is acknowledged. The traversal is on the ground(s) that "the present case poses no search burden what so ever because complete search on all adenosine receptor targets, compositions and uses was done in U.S. Patent Applications Serial Nos. 08/472,527, 08/757,024, and 08/474,497, by examiner Hauda. Moreover, the examiner in those cases did not see necessary to separate them into bits and pieces to lighten up her docket".

This is not found persuasive because the restriction requirement was deemed necessary because claims 1-64 where drawn to a product and claims 65-107 were drawn to methods of use of said product (MPEP 806.05(h)). According to Applicant's representative, a search of the nucleic acid molecules claimed in the instant application was already performed by examiner Hauda, however the claimed compositions where new and novel because of the presence of a "surfactant". However, a new search of the 900+ nucleic acid molecules of the instant invention was deemed necessary since the instant application does not claim priority to the other applications submitted by the inventor of the instant application, therefore there was no apparent reason to assume that the claimed sequences of the instant invention where identical to the sequences previously searched in the previous applications submitted by the inventor. Moreover, since adenosine receptors A_1, A_{2B}, and A_3 (A_{2A} as well), are independent genes, which are transcribed into chemically different mRNA molecules each having a unique three dimensional folding patterns and different accessible sites for forming a hybridization complex with an antisense oligonucleotide, the antisense molecules designed to target these individual genes would comprise a patentably distinct inventions. For this reason the applicant is required to elect a patentably distinct invention. The requirement is still deemed proper.

However, in order to speed up the examination of this application, and in light of the PTO practice that allows an Applicant to rejoin restricted process claims to an elected invention once allowable product claims have been identified in an application, the examiner will withdraw the restriction requirement of the instant application and will examine all the claims as a single invention.

Specification

4. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 250 words. It is important that the abstract not exceed 250 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

Claim Objections

5. Claim 8 limits the composition of claim 1 to having one (and only one) substituted A. Claim 9 is drawn to the composition of claim 8 wherein all (A)s are substituted. Claim 9 fails to further limit claim 8.

Explain surf. not carrier. & explain role

6. Claim 25-28 recite the limitation "further comprising a carrier", this limitation fails to further limit claim 1. The claimed limitations of claims 25-28 are inherently present in claim 1, since claim 1 recites a "pharmaceutical composition, comprising a surfactant".

7. Claim 30 recites the limitation " the nucleic acid, the surfactant, a therapeutic agent and a

pharmaceutically acceptable carrier", this limitation fails to further limit claim 29. The claimed limitations are inherently present in claim 29. Claim 29 recites: a pharmaceutical composition comprising a surfactant, a nucleic acid, and a therapeutic agent.

8. Claim 83 recites "wherein the subject is an animal", this limitation does not further limit claim 81, since claim 81 requires that the subject be a mammal.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-107 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

11. Claims 1 and 57 (and all claims dependent thereof) recite "the oligo being selected from the group consisting of oligonucleotides which are antisense to target genes and mRNAs corresponding to the target genes, to genomic flanking regions selected from the group consisting of...;" The metes and bounds of this Markush group is unclear because it is unclear if the members of this group are mutually exclusive, furthermore the individual members of the Markush group are not clearly delineated. Furthermore, it is uncertain if Applicant intends the oligonucleotide to be an antisense to target genes, an mRNA corresponding to the target genes, or mRNAs corresponding to genomic flanking regions. The meaning of the phrase "genomic flanking regions" is vague and indefinite since

it is unclear what exact genomic sequence Applicant is referring to, particularly it is unclear as to what gene Applicant is referring to. As written the claim is referring to any genomic flanking region to any gene as long as it is effective to alleviate bronchoconstriction, allegy (ies) or inflammation.

12. Claims 1 and 57 (and all claims dependent thereof) recite the term "allegy (ies)", this term is vague and indefinite since it is unclear as to what the meaning of this word is. Applicant probably meant to use the term "allergy (ies)" instead.

13. Claims 1 and 57 (and all claims dependent thereof) recite "combination of the oligos; pharmaceutically acceptable salts of the oligos; and mixtures of the oligos, their combinations and their salts." Applicants are referring to multiple oligos, it is unclear as to what other oligos Applicants are intending to claim.

14. Claims 1 and 57 (and all claims dependent thereof) recite "the oligo being selected from the group consisting of oligonucleotides which are anti-sense to target genes and mRNAs corresponding to the target genes, to genomic flanking regions selected from the group consisting of...; anti-sense to target genes....., and consists of less than about 15% adenosine (A); combinations of the oligos; pharmaceutically acceptable salts of the oligos; and mixtures of the oligos, their combinations and their salts". The overall Markush group recited in claim 1 is vague and indefinite since it unclear as to whether the individual components within each internal Markush group are to be considered mutually exclusive.

15. Claims 6-7 recite "wherein the target gene is selected from the group consisting of", neither element in the Markush groups of these claims represent "target genes" except the term "target gene" in each group. The claims do not clearly set forth what "target gene" applicant is referring to. Applicant most likely intended the claims to recite "target nucleic acid sequences". Claims 6-7 recite the phrase "mRNAs and bridging sections thereof of the adenosine ...receptor". This phrase is vague and indefinite since the metes and bounds of the meaning of the term "bridging sections thereof" is unclear. [Minor claim objection: claims 6-7 recite " target genes, , sequences", the additional comma used here should be removed.]

16. Claims 11, and 98 recite "wherein the pyrimidines and purines are substituted at a position selected from the group consisting of positions 1, 2, 3, 4, 7, and 8. The exact positions of substitution that Applicant is referring to are vague and indefinite since is unclear where these positions are in both pyrimidines and purines, pyrimidines and purines are different classes of molecules with different positions that are potentially substituted.

17. Claims 15 and 16 recite "wherein..linking phosphodiester residue..selected from the group consisting of methylphosphonate, phosphotriester...and combinations thereof". Neither element in the Markush group represent phosphodiester linkages, the elements of this group represent different classes of modified internucleoside linkages.

14. Claim 18 recites "the composition of claim 1, wherein the anti-sense oligonucleotide

comprises SEQ ID NOS: 1, 3, 5, 7, and fragments 1-957 (SEQ. ID NO: 8-957) of SEQ. ID NO: 7, and SEQ. ID NOS: 953-996." This claim is an improper Markush group, the elements of this group should be separated by an "or" instead of "and". It is also unclear how SEQ ID NO: 8-957 (only 949 sequences) can represent "fragments 1-957" recited by Applicant.

15. Claims 19-20 recite "cell internalized or up-taken agent", these claims are vague and indefinite since the metes and bounds of what this recited phrase means is unclear.

16. Claim 23 recites "artificial lamellar bodies vehicles for surfactant components", which is vague and indefinite, the metes and bounds of this phrase is uncertain.

17. Claim 23 contains the trademark/trade name BRIJ35, TRITON-X, ALEC, SURVANT, EXOSURF, ATOVAQUONE. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112, second paragraph. See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. In the present case, the

trademarks/trade names are used to identify/describe surfactants and, accordingly, the identification/description is indefinite.

18. Claim 29 recites the limitation "other therapeutic agents" in claim 25. There is insufficient antecedent basis for this limitation in this claim. In addition, the recited limitations are vague and indefinite since it is unclear what "other" agents Applicant are referring to.

19. Claim 31 there is no antecedent basis for "other anti-adenosine receptor agents, and other anti-arrhythmic agents". Furthermore, the recited limitations are vague and indefinite since it is unclear what "other" agents Applicant is referring to.

20. Claim 45 recites "iontophoretic transdermal formulation" , for which there is no antecedent basis in claim 36.

21. Claim 50 recites "the formulation of claim 49, wherein the vesicles comprise liposomes, and the particles comprise microcrystals", there is insufficient antecedent basis for this limitation in the claim since claim 49 recites only a carrier which comprises either vesicles or particles, but not both.

22. Claims 55-56 are vague and indefinite, since Applicant has not defined what a unit of the

formulation of claim 36 is, neither has Applicant defined what quantity of formulation constitutes a formulation "in bulk".

23. Claim 58 recites "and optionally and optionally", this statement is most likely a typographical mistake. Claim 58 also recites "other diagnostic agents", there is no antecedent basis for this limitation in this claim since Applicants have not specified what the "other" agents are.

24. Claim 62 recites "other anti-adenosine receptor agents", there is no antecedent basis for this limitation since it is unclear as to what Applicant refers to as "other" agents.

25. Claims 66-67, 72-74 and 77 recite the limitation "the disease or condition" in claim 65. There is insufficient antecedent basis for this limitation.

26. Claim 67 recites "wherein the disease or condition is selected from the group consisting of pulmonary vasoconstriction.....to test cardiovascular function, ...and those which are treated with radiation, chemotherapeutic, antibody therapy and phototherapeutic agents." The overall Markush group recited here is vague and indefinite since it is unclear if the individual components within this Markush group are to be considered mutually exclusive.

27. Claim 69 recites "the adenosine receptor mRNA" and "the adenosine receptor", for which

there is insufficient antecedent basis in claim 65.

28. Claim 72 recites "the lung airways", for which there is insufficient antecedent basis in claim 65.

29. Claim 75 recites the limitation "the therapeutic agent" in claim 74. There is insufficient antecedent basis for this limitation in this claim. Furthermore, claim 75 recites "other adenosine A, A2B, A3 receptor inhibiting agents" and "other anti-arrhythmic agents", this phrase is vague and indefinite since Applicant does not clearly define what the "other" agents are. The overall Markush group recited in claim 75 is vague and indefinite since it is unclear if the individual components within this Markush group are to be considered mutually exclusive.

30. Claim 76 recites the limitation "the therapeutic agent" in claim 65. There is insufficient antecedent basis for this limitation in this claim.

31. Claim 81 recites the limitation "mammals" in claim 80. There is insufficient antecedent basis for this limitation in this claim. In addition, claim 81 recites "wherein the mammals are selected from the group consisting of humans and animals", this is an improper Markush group because humans and animals do not represent mutually exclusive groups. Furthermore, animals is completely inclusive of both humans and mammals.

32. Claim 89 recites "nucleic acids selected from the group consisting of G and C", this phrase is improper since G and C are nucleotide bases and are not considered nucleic acids.

33. Claim 90 recites the limitations " the method" in claim 61. There is insufficient antecedent basis for these limitations in this claim. Furthermore claim 61 is a product claim, not a method claim.

34. Claim 94 recites the limitation "the adenosine receptor target" in claim 65. There is insufficient antecedent basis for this limitation in this claim.

35. Claim 95 recites the limitation "wherein at least one A is substituted". This phrase is vague and indefinite since it unclear which "A" the Applicant is referring to since the method of claim 65 does not refer to an "A" in the claim.

36. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

37. Claims 1-107 are rejected under 35 U.S.C. 112, first paragraph, because the specification,

while being enabling for pharmaceutical compositions comprising antisense oligonucleotides effective in treating an asthmatic condition provoked by the administration of adenosine, does not reasonably provide enablement for the treatment of any and all airway diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-107 are drawn to "a pharmaceutical composition comprising a surfactant; and a nucleic acid which comprises an oligonucleotide (oligo) effective to alleviate bronchoconstriction, allegy (ies) or inflammation, the oligo being selected from the group consisting of oligonucleotides which are anti-sense to target genes and mRNAs corresponding to the target genes....", *in vivo* methods of delivery and kits comprising said pharmaceutical compositions. Due to the vagueness and indefiniteness of the claim language used herein, this claim can be interpreted as reading on pharmaceutical compositions comprising a nucleic acid which comprises an oligonucleotide effective to alleviate bronchoconstriction, allergies, or inflammation, which are antisense oligonucleotides to any target gene and mRNAs corresponding to the target gene.

The specification as filed discloses only antisense oligonucleotides targeting mRNAs encoding adenosine receptors There are no guidelines or instruction to teach one of skill in the art to make and or use a pharmaceutical composition, comprising a surfactant and an antisense targeting any and all genes, to alleviate bronchoconstriction, allergies or inflammation. The specification discloses only functional antisense targeting adenosine receptors in aerosolized form that are effective in alleviating

bronchoconstriction, allergies and inflammation.

The specification fails to provide an enabling disclosure for how to treat bronchoconstriction, inflammation, and allergies, by the administration of a pharmaceutical composition comprising an antisense oligonucleotide targeting any gene and a surfactant. In the absence of a comprehensive understanding of the role of a particular gene product in the etiology of a given disease state, it is impossible to predict if the inhibition of that gene product would yield any useful or efficacious results. Furthermore, even if the role of a given gene product is well understood, due to the unpredictability regarding the behavior of antisense based therapeutics that one cannot predict whether an oligonucleotide targeted to the gene in question would effectively reduce its expression *in vivo*. The design of antisense oligonucleotides to a target gene requires knowledge of the nucleic acid structure of the gene, the specification as filed provides description of nucleic acids targeting adenosine A1, A2B, and A3 receptor mRNAs. Crooke describes a variety of factors that influences the activity of antisense based compounds that must be considered when designing an antisense oligonucleotide. Crooke teaches that variations in cellular uptake and distribution of antisense oligonucleotides are influenced by a variety of factors such as: length of the oligonucleotide, modifications to the oligonucleotide structure, the nucleotide sequence of the oligonucleotide and the type of cell the antisense is administered to. Furthermore, Crooke describes the influence of non-antisense effects, for example, phosphorothioate oligonucleotides tend to bind to many proteins, this protein binding may influence cell uptake, distribution, metabolism and excretion of the

oligonucleotide. Such protein binding may produce effects that can be mistakenly interpreted as antisense activity, and such binding may also inhibit antisense activity of some oligonucleotides. In addition to proteins, oligonucleotides may interact with other biological molecules, such as lipids, or carbohydrates, and such interactions, like those with proteins , will be influenced by the chemical class of oligonucleotide studied (Crooke, 1998; p. 3). Crooke clearly teaches that there is a significant level of factors which influence the behavior of antisense based compounds thereby rendering the activity of antisense compounds unpredictable.

38. Claim 87 , reads on an *in vivo* method of delivering a pharmaceutical composition to a target polynucleotide, comprising administering to a subject the composition of claim 1, comprising an amount of the surfactant and of the nucleic acid effective to reach the target polynucleotide, wherein said method is a prophylactic method.

The prophylactic method of claim 87 reads on a method to prevent the development of a disease or condition in a subject. The specification as filed does not teach how a disease could be prevented by administration of the pharmaceutical composition of claim 1 to a subject. It is not clear from the specification whether the therapy to prevent recited here would have started months ahead or days ahead of a probable expectation of disease, if there is a particular amount of the formulation that needs to be administered, or if a particular treatment regimen is necessary. In addition, the specification does not teach how long such a treatment must be continued in order to prevent the development of a disease or condition. Further, Applicant has only shown that one of skill in the art

would expect the incidence of disease to be reduced, not completely prevented.

The specification as filed does not enable anyone of skill in the art to practice the instant invention throughout the full scope of the claimed invention. This conclusion is based upon the known unpredictability in the art regarding the behavior of antisense compounds and methods of prevention, the lack of guidance and/or direction provided by the specification, the limited number of working examples, the breadth of the claims, and the amount of experimentation need to practice the invention.

39. Claims 8-13 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for substituting Adenosine (A) into the nucleic acid of claim 1 with heteroaromatic bases such as theophylline, caffeine, dyphylline, etophylline, acephylline piperazine, bamifylliline, enprofylline, and xantine (or xanthine), wherein the base has antagonistic activity against the adenosine receptor (Examiner's interpretation of the claim), does not reasonably provide enablement for substituting (A) with all of the heteroaromatic bases described by the Applicant, wherein said base has antagonistic against adenosine receptors A1, A2b, and A3; no activity; or have agonistic activity at the adenosine A2a receptor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 8-13 are drawn to a pharmaceutical composition comprising a surfactant and a nucleic acid which comprises an oligonucleotide effective to alleviate bronchoconstriction, allergies, or

inflammation, wherein the oligo is an antisense oligonucleotide targeted to target genes and mRNAs corresponding to target genes, including mRNAs encoding adenosine receptors A1, A2b and A3 receptors, which may be substituted by a "universal base" which binds to a thymidine base but have antagonist activity at the adenosine receptors A1 A2b and A3 receptors.

The prior art teaches that xanthine analogs, such as caffeine, theophylline, and enprofylline are potent antagonist of adenosine receptor activity and function as a tracheal relaxant and have an anti-asthmatic effect. However, it also teach that certain analogs of these compounds behave differently than the parent compounds, and that each compound had to be independently studied in order to determine their ability to modulate adenosine receptor function. The specification as filed and the prior art (see Brackett et al.) provides evidence of the function of a limited number of compounds that modulate the activity of adenosine receptors, however the specification as filed provides little or no guidance in how to determine or predict the behavior of the enormous number of heteroaromatic "universal bases" that can substitute (A) in the nucleic acid of claim 1 of the instant application as recited in claims 8-13, and still maintain its claimed function. Namely, wherein said nucleic acid which comprises and oligonucleotide is effective to alleviate bronchoconstriction, allergies, or inflammation. Nor does the specification as filed teach how to synthesize antisense oligonucleotides containing nucleotides that are substituted by the claimed heteroaromatic bases.

The specification as filed does not enable anyone of skill in the art to practice the instant invention throughout the full scope of the claimed invention. This conclusion is based upon the

unpredictable effect of the heteroaromatic compounds on the activity of adenosine receptors and the unpredictable behavior of antisense oligonucleotides, the lack of guidance or instruction by the specification, the limited number of examples, the extensive breadth of the claims, and the quantity of experimentation required to practice the instant invention.

Claim Rejections - 35 USC § 102

40. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

41. Claims 1-7, 15-17, 23-28, 30, 34-37, 40, 53-54, 65-75, 80-81, 83, 88-90, 94, and 102-103 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Nyce et al. (Nature Vol. 385, No. 6618, 1997, pp. 721-725), Nyce et al. (WO 9640162A1), or Nyce et al. (WO 9640266A1).

Nyce et al. (Nature) teach that aerosolized antisense oligonucleotides targeting the A1 receptor mRNA reduced the number of adenosine A1 receptors in smooth muscle tissue (P. 723). Nyce et al. performed a randomized cross over study using the dust- mite conditioned allergic rabbit model of human asthma. Administration of an aerosolized phosphorothioate antisense oligodeoxynucleotide targeting the adenosine A1 receptor desensitized the animals to subsequent challenge with either adenosine or dust-mite allergen. An antisense oligonucleotide having the

following sequence: "GATGGAGGGCGGCATGGCGCC" (about 14% A) was used in DNA antisense therapy for asthma in an animal, this antisense oligonucleotide is identical in sequence to the antisense oligonucleotide comprising SEQ ID NO: 1 of the instant application.

Nyce et al. teach each and every aspect of the instant invention thereby anticipating Applicant's claimed invention.

Nyce et al. (WO 9640162A1), teach a method of treating airway disease in a subject comprising topically administering an antisense oligonucleotide to the airway epithelium of said subject in an amount effective to treat said disease, and wherein said oligonucleotide being essentially free of adenosine, and further wherein said antisense oligonucleotide is targeted against an mRNA encoding a protein selected from the group consisting of human A2a adenosine receptor, human A2b adenosine receptor, human IgE receptor b, human Fc-epsilon receptor, CD23 antigen, human histidine carboxylase, human beta tryptase, and several other genes (p. 60-61). Nyce et al. discloses pharmaceutical compositions comprising an antisense oligonucleotide in an amount effective to treat an airway disease in a pharmaceutically acceptable carrier, wherein said antisense oligonucleotide comprises nucleotides in which at least one phosphodiester linkage is replaced with a linkage selected from the group consisting of methyphosphonate linkages, phosphotriester linkages, phosphorothioate linkages, phosphorodithioate and phosphoroamidite linkages (p. 62). Furthermore, Nyce et al. disclose phosphorothioate modified antisense oligonucleotides comprising the sequence according to SEQ ID NO: 1, 3, and 5 of the instant application.

Nyce et al. (WO 9640266A1) teach adenosine receptor antisense oligonucleotides that hybridize to any coding sequence in an mRNA which codes for the A1 adenosine receptor or A3 adenosine receptor, and upon hybridization causes a decrease in gene expression of the A1 or A3 adenosine receptor (p. 6). The antisense oligonucleotides disclosed by Nyce et al. may have a sequence comprising SEQ ID NO: 1, 3, and 5 of the instant application (p. 7), and wherein the oligonucleotides include modified internucleoside linkages including: methylphosphonate, phosphotriester, phosphorothioate, phosphorodithioate, and phosphoramidate linkages, and modifications that protect the oligonucleotide from nuclease degradation (p. 7). The oligo-nucleotides may be of any suitable length depending on the particular target being bound and the mode of delivery, wherein the antisense oligonucleotide is preferably directed to an mRNA region containing a junction between intron and exon, to a region sufficiently close to the junction to inhibit mRNA splicing, or they may be targeted to the initiation codon (p. 8-9). Nyce et al. also teaches pharmaceutical compositions comprising the above antisense oligonucleotides and a suitable pharmaceutically acceptable carrier, including both aerosol and surfactant formulations (p. 9-13). Nyce et al. disclose a method of reducing adenosine-mediated bronchoconstriction in a subject in need of such treatment, comprising administering an adenosine receptor antisense oligonucleotide to the lungs of the subject in an amount effective to reduce bronchoconstriction, wherein said adenosine receptor is either the A1 or A3 adenosine receptor (p. 24), and further wherein said antisense oligonucleotides comprise the sequence of SEQ ID NO: 1, 3, and 5 of the instant application.

42. Claims 1-7, 10, 14-18, 23-28, 30, 34-37, 40, 53-54, 65-75, 80-81, 83, 88-90, 94, and 102-103 are rejected under 35 USC 102(b) as being clearly anticipated by Stiles et al.

Stiles et al. teach antisense oligonucleotides having a sequence capable of binding specifically with any sequence of an mRNA molecule which encodes a human A adenosine receptor so as to prevent translation of the mRNA molecule. The antisense oligonucleotide may have a sequence that contains chemical analogs of nucleotides, e.g., nucleotides in which the phosphodiester bonds have been modified to a methylphosphonate, phosphotriester, or phosphoramidite, so as to render the oligonucleotides more stable in vivo. Antisense oligonucleotides may be of any suitable length, for example from about 10 to 60 nucleotides in length depending upon the particular target being bound and the mode of delivery thereof. Preferably the antisense oligonucleotide is directed to an mRNA region containing a junction between intron and exon. Where the antisense oligonucleotide is directed to an intron/exon junction, it may either entirely overlie the junction or may be sufficiently close to the junction to inhibit splicing out of the intervening exon during processing of precursor mRNA to mature mRNA, for example with the 3' or 5' terminus of the antisense oligonucleotide being positioned within about, for example, 10, 5, 3, or 2 nucleotides of the intron/exon junction. Stiles et al. also teach pharmaceutical compositions comprising an antisense oligonucleotide as given above effective to reduce expression of human A1 adenosine receptor in a cell so as to prevent its translation. The antisense oligonucleotides may be formulated with a hydrophobic carrier capable of passing through a cell membrane. The oligonucleotides may also be coupled to a substance which

inactivates mRNA, such as a ribozyme. Such oligonucleotides may be administered to a subject to inhibit the activation of A1 adenosine receptors, which subject is in need of such treatment.

Stiles et al. teach each and every aspect of the instant invention thereby anticipating Applicant's claimed invention.

43. Claims 1-7, 15-17, 23-28, 30, 34-37, 40, 53-54, 65-75, 80-81, 83, 88-90, 94, and 102-103 are rejected under 35 U.S.C. 102(b) as being anticipated by US Patent No. 5,514,788 (1996) Bennett et al.

Claims 1-7, 15-17, 23-28, 30, 34-37, 40, 53-54, 65-75, 80-81, 83, 88-90, 94, and 102-103 are drawn to pharmaceutical compositions comprising a surfactant, and an antisense oligonucleotide effective to alleviate bronchoconstriction, allergies, or inflammation.

Bennett et al. teach a method of treating diseases, including asthma (see Abstract and col. 3, lines 15-18), and a pharmaceutical composition for use in such a method, comprising administration of antisense oligonucleotides targeted against an mRNA encoding ICAM-1, VCAM-1, or ELAM-1 (see col. 5, lines 21-29); the antisense oligo, which may comprise nucleoside linkages such as phosphorothioates, phosphotriesters or methyl phosphonates and contains approximately 10% adenosine, may be administered topically, by inhalation, in a formulation that may include sprays (col. 7, lines 44-53).

Therefore, Bennet et al. teach each and every aspect of the instant invention thereby anticipating Applicant's claimed invention.

44. A person shall be entitled to a patent unless --

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

45. Claims 1-107 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Nyce et al. (US 5,994,315).

Nyce et al. disclose pharmaceutical compositions for alleviating bronchoconstriction or lung inflammation when administered to a mammal, comprising an antisense oligonucleotide to the initiation codon, the coding region or the 5' or 3' intron-exon junctions of a gene encoding an adenosine A1 receptor, adenosine A2a receptor, adenosine A2b receptor, or adenosine A3 receptor, or antisense to their respective mRNAs, and a pharmaceutically acceptable carrier. The pharmaceutically acceptable carrier may be an aerosol formulation, or further wherein said composition comprises an agent selected from the group consisting of antioxidants, flavoring agents, volatile oils, buffering agents, dispersants, surfactants, propellants and preservatives. Nyce et al. also disclose methods of alleviating an airway disease or condition associated with adenosine receptor mediated bronchoconstriction or lung inflammation comprising administering to a subject antisense to the coding region of a gene encoding an adenosine receptor selected from the group consisting of A_1, A_{2A}, A_{2B}, and A_3 receptor mRNA, wherein said antisense oligonucleotide has at least residue selected from the group consisting of methyphosphonate, phosphotriester, phosphorothioate,

phosphorodithioate, boranophosphate, formacetal, thioformacetal, thioether, carbonate, carbamate, sulfate, sulfonate, sulfamate, sulfonamide, sulfone, sulfite, sulfoxides, sulfide, hydroxylamine, methylene, methylenoxy, and phosphoramidate residues.

Nyce et al. teach each and every aspect of the instant invention, thereby anticipating applicant's claimed invention.

Claim Rejections - 35 USC § 103

46. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

47. Claims 8-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nyce et al. in view of Jacobson et al.

Claims 8-13 are drawn to a pharmaceutical composition comprising a surfactant and a nucleic acid which comprises an oligonucleotide effective to alleviate bronchoconstriction, allergies, or inflammation, wherein the oligo is an antisense oligonucleotide targeted to target genes and mRNAs corresponding to target genes, including mRNAs encoding adenosine receptors A1, A2b and A3 receptors, which may be substituted by a "universal base" which binds to a thymidine base but have antagonist activity at the adenosine receptors A1 A2b and A3 receptors, and further wherein said base

has no activity, or have agonistic activity at the adenosine A2a receptor.

Stiles et al. teach the design of antisense oligonucleotides targeting adenosine receptors as described above, however et al. does not teach the substitution of an adenosine base with a base that has antagonistic activity at adenosine receptors.

Brackett et al. teach that a variety of xanthines cause tracheal relaxation, an activity predictive of anti-asthmatic potential. Specifically, Brackett et al. examined the behavior of structural analogs of caffeine, theophylline, and enprofylline. This study revealed chemical analogs of these compounds that were significantly more potent tracheal relaxers than the parent compounds, however they also identified some structural analogs that were less potent relaxers than the parent compounds.

Double Patenting

48. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321 (C) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground

provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

49. Claims 1-107 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-105 of U.S. Patent No. 5,994,315 (US Patent Application 08/474,497), and all claims of both US Patent Application 08/472,527, and 08/757,024.

Although the conflicting claims are not identical, they are not patentably distinct from the claims of US Patent No. 5,994,315, since the issued patent, pending applications and the instant application disclose and claim pharmaceutical compositions and methods of treating a subject for airway disease comprising the administration of antisense oligonucleotides targeting adenosine receptors in a pharmaceutically acceptable carrier. The pharmaceutical composition of the instant invention comprises a surfactant in combination with antisense targeting adenosine receptors, the invention of Nyce et al. read on the same basic subject matter however, the use of an aerosol formulation is emphasized, however the pharmaceutical composition of the published patent also further comprises a surfactant, see claim 30. US Patent No. 5,994,315 also includes a method for *in vivo* delivery of an oligonucleotide to a target adenosine receptor polynucleotide, comprising administering into a mammalian subject's respiration an aerosol of the composition of claim 1, comprising an amount of the adenosine receptor oligo effective to reach the target adenosine receptor

polynucleotide (claim 69 and dependent claims 70-105), overlapping subject matter is observed in the instant application, claims 65 and dependent claims.

US Patent Application 08/472,527 discloses a method of reducing bronchoconstriction in a subject comprising the administration of an antisense oligonucleotide molecule directed against the A1 or the A3 receptor in an amount effective to reduce bronchoconstriction. This application also discloses methods of treating patients afflicted with asthma, and pharmaceutical formulations. The antisense oligonucleotides used in the methods described in this Application include antisense oligonucleotides comprising the sequence according to SEQ ID NO: 1, 3, and 5 of the instant application.

US Patent Application 08/757,024 discloses all of the antisense oligonucleotide structures targeting adenosine receptors recited in the instant application, modified antisense oligonucleotides, pharmaceutical compositions and formulations comprising said antisense oligonucleotides in a carrier (including aerosols, lipid particles, hydrophobic carriers), kits comprising said antisense oligonucleotides, a delivery device and instructions for use, and methods for treating a disease condition associated with bronchoconstriction and/or lung inflammation, and allergies. All aspects of the invention of 08/757,024 encompass the invention recited in the instant application.

Therefore, the invention as a whole is obvious over US Patent No. 5,994,315, and US Applications 08/472,527 and 08/757,024.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps whose telephone number is (703) 308-8883. The examiner can normally be reached on Monday through Friday from 8:30 AM to 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, George Elliott, can be reached at (703) 308-4003. The fax number for this group is (703) 305-7939.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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January 3, 2000